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| 10/533,697 | 05/03/2005 | Sylvain Rault | SERVIER 457 PCT | 6150 |

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| EXAMINER |
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JAISLE, CECILIA M

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| ART UNIT | PAPER NUMBER |
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1624

DATE MAILED: 08/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/533,697

Applicant(s)

RAULT ET AL.

Examiner

Cecilia M. Jaisle

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2005 and 25 May 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 29-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 29-37 is/are allowed.
- 6) ☒ Claim(s) 38-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>03 May 2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific compounds of Examples 1-16 as hypolipaemic agents (pages 12-13), does not provide reasonable enablement for the breadth of the claimed Formula (I) compounds for the various disorders listed at pages 1 and 5-13, including those yet to be identified, as due to modulation of kinase activity. The following reasons apply.

Claims 38-42 are drawn to alleviation of various diseases said to be associated with kinase activity. The claimed compounds are shown to be hypolipaemic (hypolipidemic) agents in obesity-associated insulin resistant mice (page 12), however, the specification asserts that the claimed compounds are useful to alleviate all diseases associated with kinase activity, such as all the diseases recited for claims 38-42, for which the specification provides no competent evidence. The specification provides no factual basis for the assertion that all of the claimed compounds modulate kinase activity, what kinases are modulated, what kinase activities are involved, nor whether such modulation involves inhibition or potentiation of kinase activity. The single test showing that the claimed compounds have hypolipaemic activity in obesity-associated

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insulin resistant mice (page 12) offers no evidence establishing any connection with the illustrated hypolipemic activity and any other specific activity of any other specific kinase. The kinase screening (page 12) provides no identification of the specific kinases screened, the specific screening procedures used, any correlation between any specific compound of the present invention and a specific kinase, any correlation between any specific kinase activity and a specific disease/condition associated therewith, or any indication whether the individual tested compound exhibited a potentiating or inhibiting effect in regard to a specific kinase activity. The On-line Medical Dictionary for the Centre for Cancer Education at the University of Newcastle upon Tyne defines kinase as an abbreviation for phosphokinase or phosphotransferase, which in turn is defined as simply an enzyme, a "protein molecule produced by living organisms that catalyses chemical reactions," having six main groups. There is no indication that the testing reported in the present specification is in any way commensurate in scope with the broadest meaning of kinase.

The medical literature supports that there is a specific empirically-determinable correlation between a kinase activity and a disease/condition; that the identification of an agent that modulates the activity of a specific kinase cannot support a generalized conclusion that that agent will alleviate kinase-activity in regard to other diseases/conditions. Goueli illustrates that specific kinases are implicated in only certain specific diseases/conditions (col. 1, lines 36-45):

[A]n enzyme assay for abnormal levels of the enzyme creatine kinase in the blood is ... a diagnostic measure of heart disease. ... [B]one or liver diseases can be diagnosed by ... levels of alkaline phosphatase [a kinase]

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in the blood stream. Prostate cancer is diagnosed by increased levels of acid phosphatase [a kinase] in the blood stream.

Gilbert, et al. determined that protein kinase R is implicated only in the cartilage degradation that occurs in arthritic disease. Rask-Madsen, et al. concluded that protein kinase C is at best only partially involved in early events in atherogenesis. Leng, et al. show that even members of the same kinase family have different properties; catalytic and non-catalytic functions in a single WNK kinase are not uncommon.

Many if not most diseases said to be prevented or controlled by the claimed compounds, cancer, non-insulin-dependent type II diabetes, etc., are known as difficult to treat. Although the present specification asserts that all of the claimed compounds modulate kinase activity, the only hypolipaeamic activity is demonstrated. Substantiation of the method of use is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* The disclosure in this application is not sufficient to enable the instant method claims based solely on anti-hypolipaeamic activity. The state of the art, as exemplified by the references discussed *supra*, is indicative of the requirement for undue experimentation.

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Thus, ability of a compound that modulates kinase activity to prevent or ameliorate all of the diseases/conditions recited by the present claims remains open to proof.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. Breadth of the claims: The claims embrace a variety of diseases/conditions, including ones yet to be determined, related to modulation of kinase activity.
2. Nature of the invention: Therapeutic use of the claimed compounds in preventing and treating diseases/conditions by modulation of kinase activity.
3. State of the prior art: See the discussion of references *supra*.
4. Level of predictability in the art: Applicants do not provide highly predictive competent evidence or recognized tests to prevent and treat all conditions recited

for the claimed compounds. Pharmacological activity in general is unpredictable.

In applications involving physiological activity, such as the present,

“The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.”

Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (Fed.Cir. 2003).

5. Amount of direction provided; and (6) presence of working examples: The specification working examples do not show prevention and treatment of all conditions. The state of the art (e.g., references discussed above) supports that successful prevention and treatment of diseases/conditions related to modulation of kinase activity is empirically determined and subject to further investigation.
7. Quantity of experimentation needed to make or use the invention, based on the content of the disclosure, would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.

The consideration of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the breath of the claims, the pharmaceutical nature of the invention, the unpredictability of relationship between kinase activity modulation and specific diseases/conditions, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

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The Supreme Court has recognized that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 148 USPQ 689, 696 (U.S. 1966). See also *In re Genentech, Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997) ("patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.")

MPEP 2164.01(a) states,

A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration clearly justifies that conclusion here and undue experimentation would be required to practice Applicants' invention. Proper limitation of claims 38-42 to a method for the control of hypolipaemia would be seen to overcome this rejection in regard to those claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "including " renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Reasons for Allowance

Claims 29-37 are allowable. The present claims patentably distinguish from Ishida, et al., US Patent Appln. Pub. 2005/0080096, published April 14, 2005, disclosing condensed heterocyclic compounds as useful, inter alia, in the treatment of diabetes. Example 5 of Ishida, et al. prepared 2-{3-[4-(4-fluorophenyl)-3,6-dihydro-1(2H)-pyridyl]propyl}-pyrido[2,3-d]pyrimidin-4(3H)-one and Example 6 of Ishida, et al. prepared 6-methyl-2-[3-(4-fluorophenyl)-3,6-dihydro-1(2H)-pyridyl]propyl]-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4(3H)-one, which compounds are each distinct from the compounds of the present claims 29-37 both structurally and in terms of their properties.

Conclusion

Claims 1-28 have been canceled. Claims 29-42 are pending. Claims 29-37 are allowable. Claims 38-42 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Cecilia M. Jaisle, J.D.


DEEPAK RAO
PRIMARY EXAMINER